DISSERTATION ON

CERVICAL RIPENING PRIOR TO FIRST TRIMESTER TERMINATION OF PREGNANCY - COMPARITIVE STUDY BETWEEN ISOSORBIDE MONONITRATE AND MISOPROSTOL

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CERTIFICATE

This is to certify that the dissertation entitled **"DISSERTATION ON CERVICAL RIPENING PRIOR TO FIRST TRIMESTER TERMINATION OF PREGNANCY - COMPARITIVE STUDY BETWEEN ISOSORBIDE MONONITRATE AND MISOPROSTOL"** is the bonafide original work of **Dr. P.MANJULA,** done by her under my guidance in partial fulfillment of the requirements for MD (Obstetrics and Gynaecology) branch II examination of The Tamilnadu Dr. M.G.R. Medical University to be held in March 2010. The period of post graduate study and training was from May 2007 to February 2010. I forward this to the Tamil Nadu Dr. M.G.R. Medical University, Chennai, Tamil Nadu, India.

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DISSERTATION ON

CERVICAL RIPENING PRIOR TO FIRST TRIMESTER TERMINATION OF PREGNANCY - COMPARITIVE STUDY BETWEEN ISOSORBIDE MONONITRATE (ISMN) AND MISOPROSTOL

ROLE OF MEDICAL TERMINATION OF PREGNANCY IN POPULATION CONTROL

In developing country like India can MTP show a decline in population growth?

The answer is "yes"

Induced Abortion has been practiced as a solution for unwanted Pregnancies in all countries. Given the desire in developed countries to limit families to one or two children and the efficacy of contraception in general use, it is extremely likely that any normal couple will experience atleast one unwanted pregnancy at sometime during their reproductive years. No amount of legal, religion or social restriction or lack of access to professional care will stop seeking abortions.

It was estimated that in 1995, 80 million unintended pregnancies occurred worldwide each year, of which half of this ended in abortion, resulting in a worldwide abortion rate of 35, and abortion ratio of 26.

In India in 1995-96, 5,66,500 pregnancies were terminated legally, but illegally terminated abortions are estimated to have been 12 times greater. Worldwide induced abortion is third commonest means of fertility control next to sterilizations and oral contraceptive pills.

This MTP effect of population decline could not be seen in the vast rural sector since MTP services are not freely available and practice of spacing contraceptives is not much used.

However, abortion is not accepted as a sole method of family planning but its place is great as a backup method and as a resulting method for the acceptance of contraception and sterilization.

ROLE OF MTP IN REDUCING MATERNAL MORTALITY DUE TO ILLEGAL ABORTIONS

It is estimated that out of 150,000 induced abortions that are carried out in the world everyday, one third are performed under unsafe conditions and of these 500 women die everyday. The women who turns to a lack-alley abortionists faces a 100-500 times greater risk of death. Worldwide approximately 26-31 million legal abortions and 10-22 million clandestine abortions are performed every year.

The high acceptance of illegal abortions form rural women from quacks is due to easy availability, privacy, low cost and non availability of doctors at rural hospitals and poor availability of MTP services at primary health centre.

In a study conducted in India, maternal mortality due to abortion was 12%. This can be minimized if not completely eliminated by a safe, efficient and caring family planning service accessible to all.

REVIEW OF LITERATURE

DEFINITION

Abortion:

Abortion is the termination of pregnancy, either spontaneously or intentionally, before the fetus develops sufficiently to survive. By convention, abortion is usually defined as pregnancy termination prior to 20 weeks gestation or less than 500g birthweight. Definitions vary, however, according to state laws for reporting abortions and fetal deaths.

An abortion may be spontaneous or induced. Induced abortion may be legal or illegal.

Induced abortion is the medical or surgical termination before the time of fetal viability.

First trimester termination of pregnancy means termination of pregnancy up to 12 wks of gestation.

Elective (voluntary) abortion is the interruption of pregnancy before viability at the request of the women but not for reasons of impaired mental health or fetal disease. Most abortions performed today fall into this category. Approximately one pregnancy is electively aborted for every four liver births delivered in the united states (ventura

and colleagues, 2003). The Executive Board of American college of obstetricians and gynecologist (2000) supports the right of women to choose abortion and considers this a medical matter between the women and her physician.

INCIDENCE

It is estimated that about 6 million abortions occur annually in India, of which 2 million are spontaneous and the rest are induced, of the induced abortions, only about 15% are legal and the rest are performed illegally.

Globally is approximately 46 million abortions performed of which, 26 million take place in countries where abortions are legalized.

Almost 60 percent of induced abortions were performed during the first 8 weeks and 88 percent during the first 12 wks of pregnancy. 20 percent involved women aged 19 yrs or younger and the majority were younger than 25 yrs. In 1995-96, in India abortion rate is 2.7, abortion ratio 2.1. Eastern Europe has the highest abortion rate.

LEGAL STATUS OF ABORTION IN INDIA

The induced abortion may be legal or illegal. There are many countries in the globe where the abortion is not yet legalized. In India, the abortion was legalized by "Medical termination of pregnancy Act" of 1971 and was implemented from April 1972, except in Jammu and Kashmir where it came to effect from 1 November 1976). Implementing rules and regulations were written in 1971 and revised again in 1975.
A Registered medical practitioner is qualified to perform an MTP provided,

a) One has assisted atleast 25MTP in an authorized center and having a certificate.

b) One has got six months of house surgeon training in obstetrics and gynecology.

c) One has got diploma or degree in obstetrics and gynecology.

1. Termination can only be terminated on the written consent of the women. Husband's consent is not required.

2. Pregnancy in a minor girl (below the age of 18 yrs) or lunatic cannot be terminated without the written consent of the parent or guardian.

3. Termination is permitted up to 20wks of pregnancy. When the pregnancy exceeds 12 weeks, opinion of two medical practitioners is required.

4. The abortion has to be performed confidentially and to be reported to the director of health services of the state in the prescribed form.

A variety of induced abortion services are available in India, They are

1. Government hospitals and centers

2. Municipal hospitals and maternity homes
3. Recognized non-governmental organization
4. Recognized private hospitals, Nursing home and clinics.

The indications for legal abortions are broadly grouped under the following headings.

1. Medical
2. Eugenic
3. Humanitarian
4. Social

MEDICAL OR THERAPEUTIC

To save the life of the mother.

It is indicated in

I. Cardiac disease Grade III,and IV with history of decompensation in the previous pregnancy or in between the pregnancies.
II. Chronic Glomerulonephritis
III. Malignant hypertension
IV. Cervical and breast malignancy
V. Diabetes mellitus with retinopathy
VI. Epilepsy or psychiatric illness with the advice of a psychiatrist.

EUGENIC:

When there is genetic transmission of mental Disease like downs syndrome, neural tube anomalies like anencephaly and hereditary and metabolic diseases.

It is also indicated when the fetus is likely to be deformed due to the action of drugs or exposure to viral infections or radiation.

HUMANITARIAN:

Pregnancy due to rape and pregnancy in severe mentally retarded mother.

SOCIAL:

According to WHO report, this forms the commonest indication in the present day medical practice. Pregnancy is terminated to promote not only physical or mental health but also for social well being of the pregnant women and her family.

It is limited to parous women having unplanned pregnancy with low socio economic status, pregnancy caused by rape or unwanted pregnancy due to failure of contraceptive device.

METHODS OF FIRST TRIMESTER MTP

1. MEDICAL METHODS

- ❖ Prostaglandins
- ❖ Mifepristone
- ❖ Methotrexate
- ❖ Epostane

2. SURGICAL METHODS

- ❖ Menstrual Regulation
- ❖ Dilatation and suction evacuation.
- ❖ Cervical softening prior to dilatation and suction evacuation.

MEDICAL METHODS

PROSTAGLANDINS (PG) :

There are two types of PGs for medical methods of abortion (a) misoprostol (b) gemeprost.

MISOPROSTOL:

Misoprostol is a synthetic PG analogue, developed in 1991-1992. It is inexpensive and stable at room temperature. It is used orally, sublingually and also vaginally.

a) It acts by enhancing uterine contractions and thus helping expulsion of products of conception.
b) Causes cervical softening and dilatation.

Misoprostol is not effective when used alone however when this product is used with an antiprogesterone, mifepristone (RU486), the combination has been found to be the most successful method for inducing abortion.

GEMEPROST :

Gemeprost is a PG2α Dimethl ester vaginal suppository. It is used vaginaly only for induction of abortion in combination with mifepristone or misoprostol. It is unstable, costlier and not available in India.

MIFEPRISTONE:

Synthetic steroid. Derivative of 19 Nor testosterone. Antiprogesterones are compounds that counter act action of progesterone at the receptor Site. Mifepristone also known as RU486. Mifepristone is a strong antiprogesterone and antiglucocorticoid agent with antiandrogenic antiestrogenic properties. Used in pregnancies more than 48 days, the failure rate with mifepristone increases.

COMBINATION OF DRUGS:

The International Planned Parenthood Federation (IPPF) international Medical advisory panel (IMAP) has stated that MTP up to 49 days (7 wks) is highly effective with mifepristone and misoprostol.

200mg of mifepristone followed 36-48 hours later by

1mg vaginal gemeprost (or)

800 µgm vaginal misoprostol (or)

400mg oral misoprostol up to completion of 9 weeks

METHOTREXATE:

50mg intramuscular or oral followed 5-7 days later by 800µgm vaginal misoprostol. (Repeat misoprostol 24 hours later is required)

EPOSTANE :

A progesterone blocking agent is administered in doses of 200mg every 6 hrs for 7 days.

SURGICAL METHODS

- **MENSTRUAL REGULATION**

It is the aspiration of the endometrial cavity within 14 days of missed period in a previously normal cycle when presence of early pregnancy cannot be diagnosed accurately. Menstrual regulation consists of aspiration of the content of the uterine cavity by means of the plastic cannula. It has a simple thumb operated pressure control value and piston like handle. It is independent of electricity, is portable and

washable. It has a plastic 50ml syringe capable of creating a vaccum of over 60cm of Hg. It can be done as OPD procedure. A paracervical block or sedation alone usually suffices.

The occasional complications include failure to evacuate leading to continuation of pregnancy, incomplete evacuation, haemorrhage, infection and anesthetic complications.

❖ SUCTION EVACUATION / VACCUM ASPIRATION (VA)

It is the procedure in which products of conception are sucked out from the uterus with the help of a cannula fitted to a suction apparatus. Cervix is dilated with a specially designed dilators with a guard, until adequate dilatation is achieved to permit introduction of the suction cannula of the appropriate size (diameter corresponding to the weeks of gestation). A standard negative suction of 65cm of Hg is applied and products are aspirated using a suction cannula.

ADVANTAGES:

1. Blood loss is minimal
2. Chances of uterine perforation is less.

COMPLICATIONS :

Compared to other surgical operations, legally induced first trimester termination of pregnancy is remarkably safe. The major complication rate being less than 1 in 100 procedures.

1. UTERINE HEMORRHAGE:

It occurs in 1-4% of cases, although blood transfusions are required only in 0.6 times / 1000 abortions. Haemorrhage happens more often with advanced gestational age,

when dilatation and evacuation, performed instead of vaccum aspiration and when general anaesthesia is used instead of local anaesthesia. It can be reduced by the concominant use of oxytocic drugs, during the procedure and by prior use of laminaria tent or drugs.

2. PELVIC INFECTION:

It ranges from 0.1- 1.5%. The incidence can be reduced by prophylactic use of antibiotics.

- **CERVICAL INJURY :**

It occurs in .01 to 1% cases. It happens more with dilatation and evacuation, in advanced gestational age and nulliparous women. It can be minimized to a great extent by preoperative cervical priming and dilatation.

- **UTERINE PERFORATION :**

Most dangerous but happens very rarely in 0.1 to 0.28% cases.

Uterine perforation is due to failure to identify a retroverted or retroflexed uterus. Observation alone is usually enough for a small perforation and laprotomy is needed if symptoms like fever, profuse bleeding per vaginum and signs of peritonitis persists.

- **RETAINED PRODUCTS OF CONCEPTION :**

By performing check curettage following VA incidence can be reduced.

- **CONTINUATION OF PREGNANCY :** VA fails in 1% cases. Failure is more within 2 weeks of amenorrhoea.

❖ **MATERNAL MORTALITY AND MORTIDITY :**

Morbidity rate is lowest between 7 and 8 weeks of pregnancy, after which the risk of complication rises by about 15-30% for each week of delivery.

LONG TERM COMPLICATIONS :

1. Increased chance of future abortions, prematurity, low birth weight infants.
2. Cervical incompetence
3. Slightly increased risk of sterility and ectopic pregnancy.
4. Asherman syndrome
5. Rh-iso immunization

CERVICAL SOFTENING PRIOR TO DILATATION AND SUCTION EVACUATION

Priming the cervix with prostaglandin gel or suppository atleast 4 hours earlier helps to soften the cervix so that it yields more easily, and undue force is avoided during cervical dilatation.

FEATURES OF MEDICAL AND SURGICAL ABORTION

Medical Abortion	Surgical Abortion
1. Usually avoids invasive procedure	1. invasive procedure
2. Usually avoids anesthesia	2. sedation used if desired
3. Requires two or more visits	3. usually requires on visit
4. Days to weeks to complete	4. Complete in a predictable period.
5. Available during early pregnancy	5. Available during early pregnancy
6. High success rate ~95%	6. High success rate ~99%
7. Requires follow-up to	7. Does not require follow-up in

ensure completion of abortion	all cases.
8. Requires patient participation throughout multistep process.	8. Requires participation in a single-step process.

ANATOMY OF THE CERVIX

The human cervix is an organ of diverse properties. It is a tubular connective tissue structure that has generally been considered as an inert organ playing a passive role in labour to the more active body and fundus of the uterus. During pregnancy it is rigid and preserves the growing fetus in the uterus. At term it becomes gradually soft, effaced and dilated. However it must perform quite different functions in pregnancy and labour, the nature and control of which remain an enigma.

The cervix has two openings. The internal os communicating with the uterine cavity and the external os. The length of the cervix is 2.5cm or a little more. The cervical canal is spindle shaped. The mucosa is arranged in folds and has the appearance of tree trunk with branches known as ‘arbour vitae’.

HISTOLOGY OF THE CERVIX:

The mucosa is lined by high columnar ciliated epithelium. The direction of the cilia is downwards towards the external os. The glands are racemose in type, and secrete mucus with a high content of fructose.

The cervix is mainly composed of collagen and 10% smooth muscle as opposed to the myometrium, which predominantly consists of smooth muscle.
Cervical fibroblasts are characterized by the long ‘dendrites’. Therefore connective tissue components, proteolytic enzymes and other factors secreted by the cells through the ‘dendrites’ have a relatively short diffusion distance to any point in the

tissue allowing fast remodulation of the organ.

The cervical connective tissue contains extra cellular matrix which contains both fibrillar and non fibrillar components. The fibrillar component includes collagen and elastin, proteoglycans, glycoproteins such as fibrinonectin and other proteins while the non fibrillar component contains ground substances.

The cervix predominantly composed of type I collagen (66 percent) and type III collagen (33 percent). The firmness of the cervix in the nonpregnant state is mainly due to the properties of these collagen fibrils, which are bound together in the form of bundles. These bundles are inturn embedded in ground substance consisting of proteoglycans. Proteoglycans are made of central core of proteins, which are linked to glycosaminoglycans, which are repeating disaccharide units composed of hexosamine and an uronic acid. Towards term, the glycosaminoglycan concentration of the cervix alters and the dermatan and chondroitin sulphates are replaced by hyaluronic acid, which is hydrophilic and imbibes water, which destabilizes the collagen, contributing to cervical ripening.

Cervical preparation may reduce the complications of uterine perforation and cervical injury. In addition, cervical preparation may make the length of the procedure shorter, more comfortable for the patient, and easier to perform. For these reasons, the guidelines of the Royal College of Obstetricians and Gynaecologists (RCOG) state "cervical preparation is beneficial prior to surgical abortion and should be routine if the woman is aged less than 18 years of age or at a gestation of more than 10 weeks" [RCOG 2004].

Options for cervical preparation include mechanical dilators and pharmacologic agents. Mechanical dilators are able to produce wide cervical dilation in a predictable fashion. Isaptent, the Nelaton catheter and the vibrodilator were mechanical dilators used in the past [Khanna 1980, Manabe 1981, Ng 1973]. More current methods of mechanical dilation include laminaria, Lamicel ®, and Dilapan-S TM. Pharmacologic agents such as misoprostol, gemeprost, mifepristone, sodium nitroprusside, soften the cervix and allow for easier, less forceful cervical dilation.

The ripening of the cervix resulted in softening, effacement and dispensability brought about by alterations in the biomechanical properties of the cervical tissue.

There are

a) Reduction in collagen concentration
b) Increase in water content
c) Change in glycosaminoglycans.

AGENTS USED FOR CERVICAL RIPENING PRIOR TO FIRST TRIMESTER TERMINATION OF PREGNANCY

Cervical priming not only helps is softening and further dilatation of the cervix but also reduces the chance of cervical injury and makes the procedure much easier. The cervical preparation is done by the use of either laminaria tents or drugs.

LAMINARIA TENT:

Laminaria tents are seaweeds from the stem of laminaria digitata or Japonica available in different sizes and are sterilized by keeping them in Jars containing absolute alcohol from where they can be used readily.

The tents are introduced 6-12 hrs before the operation and are removed at the time of operation. The strongly hygrospic laminaria presumably acts by drawing water from proteoglycan complexes causing the complexes to dissociate and thereby allowing cervix to soften and dilate.

Synthetic hygroscopic dilators have also been used. Lamicel is a polyvinyl alcohol polymer sponge impregnated with anhydrated magnesium sulfate (Nicolaides and co-workers 1983).

Dilapan is made of hydrogel polymer and while it was used for sometime, it is not available now in the United States. It has been claimed that it ripen the cervix more rapidly than dilators made of traditional seaweed.

The Advantages of Laminaria Test:

It decreases the incidence of cervical injury, hemorrhage and perforation.

The Disadvantages are :

- Extra time and discomfort caused by insertion
- Hourglass contracture and difficulty of removal
- Infection
- Expulsion of Laminaria tent

DRUGS

Prostaglandins :

They are 20 carbon hydroxy fatty acid with a cyclopenton ring with side chains. They are released from cell membrane phospholipids, by phospholipase A and Cyclo Oxygenase (COX) pathway. Cyclooxygenase exist in two forms. Cox-1 and Cox-2, Cox-1 is constitutive, Cox-2 is inducible responsible for inflammatory and pathological changes.

Prostaglandins causes softening and dilatation of cervix referred to as priming or ripening. At first it was assumed that prostaglandins induced uterine contractions which indirectly dilated the cervix, but now is evident that the prostaglandins especially PGE2 alter the structure of connective tissue of the cervix and makes it soft and dilated.

Prostaglandins, particularly PGE2 have a role in the physiological process of cervical ripening.

Mac Isaac and colleagues (1999) randomized women to 400µgm of misoprostol placed vaginally 4 hours before first trimester abortion versus laminaria placement. Misoprostol effected equal or greater dilatation, causes less pain on insertion and produced similar side effects.

Johnston et al (1993) have shown that the administration of PGE2 in late pregnancy provokes a rise in circulating levels of chondroitin similar to those observed in spontaneous labour, thereby supporting the concept that PGE2 may induce a breakdown of the proteoglycan complex.

Prostaglandins are well established agents for the purpose of cervical ripening in the first trimester. The various agents used are,

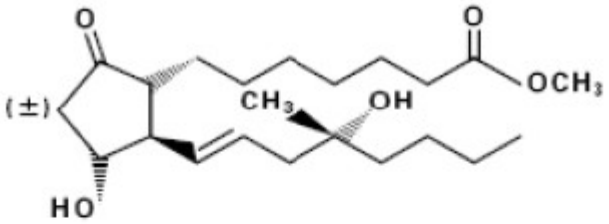
Gemeprost	1mg
Metenoprost	5mg
Misoprostol	400µg

MISOPROSTOL:

Drug Pharmacology:

PGE1, analogue orally active contains equal amount of two diasteromers presented below with their enantiomers indicated by (±:)

Molecular wt : 382.5 $C_{22}H_{38}0_5$



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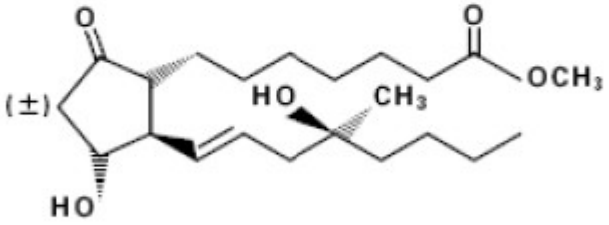


$C_{22}H_{38}O_5$ M.W. = 382.5

(±) methyl 11α,16-dihydroxy-16-methyl-9-oxoprost-13E-en-1-oate

Pharmacokinetics :

Misoprostol extensively absorbed both orally and vaginally undergoes rapid desertification, to its free acid misoprostalic acid which is responsible for its clinical activity and unlike the parent compound is detectable in plasma. The alpha chain undergoes beta oxidation and beta chin undergoes omega oxidation followed by reduction of Ketone to give PGF analogue.

Tmax – 12 + 3min (t½ life 20-40 min) serum protein binding is less than 90%

Mechanism of action :

PGs act on their own specific receptors located on cell membrance. Five major types of prostanoid receptors have been designated, each after the natural PG for which it has greater affinity. All prostanoid receptors are G.protein coupled receptors which utilize the IP3/DAG or CAMP transducer mechanisms. Misoprostol binds to EP prostanoid receptor. Rapidly absorbed after oral, vaginal and rectal administration. With oral administration the half life is less than 30 minutes and peak level is at 15 minutes. After vaginal administration, there is a gradual rise to a maximum level at 60-120 minutes, but at 240 minutes (4hrs) the level is still at 60% of peak level.

EFFECTS

The cyclic Eicosanoids produce a variety of actions depending upon the particular PG. PGs differ in their potency to produce a given action and different PGs sometime have opposite effects.

	SYSTEM	EFFECTS
1.	Gastro Intestinal System	Gastric antisecretory agent with protective effect on the gastrodeodenal muscoa
2.	Genitourinary & Renal	Increase the amplitude and frequency of uterine contractions. Stimulates total or partial expulsion of uterine contents in pregnant women.

3.	Endocrine and Gonadal effects	In some patients increases serum cortisol concentration.
4.	Respiratory Effects	Reported rare incidence of upper respiratory infections, bronchitis, bronchospasm, dyspnoea, pneumonia.
5.	Hepatic	There is elevated hepatic enzyme levels.
6.	Ocular	Reports of ocular conjunctivitis is documented.

ADVERSE EFFECTS

1.	Gastro Intestinal System	Diarrhoea 15-40% Pain abdomen 13-20%
2.	Gynecological	Spotting 0.7% Cramps 0.6% Menstrual disorders 0.3% Dysmenorrhea 0.1%

Skin :

Few adverse effects like rashes and dermatitis, alopecia noted in few patients.

Musculoskeletal:

Arthralgia, myalgia, back pain in some cases. Very few cases reported infrequently with chest pain, diaphoresis, hypertension, hypotension, arrythmias, increase in cardiac enzyme level and syncope.

Prostaglandin causes constriction defects in the distal limbs and facial deformities (mobius syndrome), and failure to induce abortion mandates termination of pregnancy surgically.

The advantages of prostaglandins are,

(1) it produces more effective cervical ripening
(2) it is more convenient to administer
(3) it can be removed in the event of hyper stimulation.

The **contraindications** can be classified as absolute and relative.

The **absolute contraindications** are hypersentivity to prostaglandins.

The relative contraindications are

1. Asthma
2. Cardiovascular disease
3. Hepatic disease
4. Previous uterine surgery

MIFEPRISTONE (ANTIPROGESTERONE):

200mg of mifepristone taken orally 46hrs before the procedure, ripens the cervix.

ISOSORBIDE MONONITRATE : NITRIC OXIDE (NO) DONOR

Organic nitrates and nitrites were introduced into medicine in the 19th century. Denitration in the smooth muscle cells release NO which is the main physiological vasodilator, normally produced by endothelial cells.

Mode of Action of Nitrates and Nitric oxide:

Both nitrates and nitric oxide activate the soluble guanylate cyclase in vascular smooth muscle cells and cause an increase in intracellular cyclic Guanosine Monophosphate (GMP) level. This is the 2nd messenger that alters calcium effluxes in the cell and induces relaxation.

Pharmacokinetics of Isosorbide Mononitrate:

Pharmacokinetic studies show that isosorbide mononitrate is rapidly absorbed after oral administration, reaches peak concentrations within an hour, undergoes no significant first-pass metabolism, and is virtually 100% bioavailable. The half-life is approximately 5 hours, the volume of distribution is 0.62 liter/kg, and the systemic clearance is 115 ml/min.

They are rapidly denitrated by glutathione reductase. The partly denitrated metabolites are less active, but have longer t½ s. Rate of absorption from the site of administration and the rate of metabolism that govern the duration of action of a particular nitrate.

The nitric oxide is basically responsible for relaxation of smooth muscles of myometrium. This is brought about by formation of NO-GMP from L-Arginine in the early pregnancy, excretion of nitrite and C-GMP plasma levels increases thereby indicating enhanced formation of NO through the action of Cyclic nitricoxide Synthase (CNOS) and L-citrulin and L-arginine. This relaxation of muscles of myometrium helps in continuation of pregnancy of till maturity.

NO in early pregnancy is detectable in high concentration and workers like All M Yallampalli et al found that in early pregnancy, the myometrial concentration of NO increases significantly but in late pregnancy there is reduction of NO in myometrium and deciduas.

The formation of NO from L-arginine is part of an intracellular communication system. The main target of this widespread system is the intracellular guanylate cyclase, which when stimulated produces cGMP from GTP. The dephosthorylation of myosin light chain kinesis (MLCK) through a cGMP dependent protein kinase. Reduced availability of phosphorylated (active) MLCK interferes with activation of myosin. It fails to interacts with actin to cause contraction consequently relaxation occurs.

Advantages of ISMN s

c) It is more stable
d) No first pass metabolism
e) Increased half life and decreased interaction variation.

NO is a free radical with a short half life. It exists in the body for 6 -10 seconds, before it reacts with water to form nitrates and nitrites. NO diffuses across cell membrane and is synthesized on demand. It is a major chemical messenger in the human body, mainly in the central nervous system. Its first discovered function was an endothelium derived relaxing factor and a primary regulator of blood pressure. NO donors relax the myometrium while inducing cervical ripening.

Tommiska M et al., studied the amount of nitric oxide in cervical fluid samples by Griess reaction in pregnant and nonpregnant women after application of misoprostol. He found misoprostol induced 4.3 to 5.2 fold elevation in cervical fluid nitric oxide concentration in early pregnancy and 4.4 to 18.2 fold elevation in late pregnancy and no effect in nonpregnant women.

No donor induced cervical ripening during pregnancy may be mediated via increased prostaglandin F2 α synthesis **(Ledingham MA et al, 1999).**

Ekerhord E et al (2002) found that analysis of tissue levels of cyclic GMP ,AMP,COX-1 and 2,PGE_2 F2α on cervical specimen fixed in glutaraldehyde for microscopy in the women scheduled for surgical termination of first trimester of pregnancy with ISMN found increased. On Eletron microscopy changes were similar to seen during spontaneous cervical ripening.

De pace V, FACCHINETTI F et al, (2007) found that NO plays a fundamental role in human physiology, being involved in the homeostasis of different functions. In obstetrics this molecule is determinant in the physiology of labour and cervical ripening and etiology of preeclampsia and IUGR.

The NO donor produces effective ripening when applied to guinea pig cervix and it is a fundamental mediator of cervical ripening. **Thomson Aj et al** concluded that the NO donor ISMN may provide an alternative for cervical ripening with fewer side

effects in the first trimester MTP.

The side effects of NO donors administered vaginally has not been described. The recognized side effects through other routes includes headache, dizziness, postural hypotension, and tachycardia.

OTHER NITRICOXIDE DONORs :

Isosorbide dinitrate, nitroglycerine and glycerol trinitrate. The potent smooth muscle relaxants affect the vasculature, gut and uterus. Their tocolytic property showed no superiority to other tocolytics **(Buhimschi, 2002; clavin; 1996)**

NO Donors have important implications for modifying vascular resistance, and thus uteroplacental blood flow during pregnancy. (Hull et al., 1994; selingman 1994) abnormal synthesis of nitric oxide has been linked to the development of preeclampsia **(Savvidon and coworkers 2003)**.

Nitric oxide therapy in term or near term infants with respiratory failure found, the nitric oxide significantly improved oxygenation. **(Finer and Barrington 2000)**.

AIM OF THE STUDY

The aim of the study is

1. To evaluate the effect of intravaginal isosorbide mononitrate for first trimester preoperative cervical ripening and to evaluate the maternal side effects if any.
2. To determine the optimum dose required to produce such an effect.
3. To compare the efficacy of intravaginal isosorbide mononitrate with that of intravaginal Misoprostol.

MATERIALS AND METHODS

-

This study was conducted at Department of obstetrics and gynecology, RSRM lying in hospital attached to Stanley Medical College. Royapuram. Chennai.

Study period : The period of study was from July 2008 to Sep 2009.

Study design : Prospective Study

Comparative Study

1. Number of Patients

200 women who were in good health and who were opting for termination of first trimester pregnancies were randomly selected from those who are attending Family welfare and antenatal outpatient department were included in the study.

Patients belonging to reproductive age from 18-40 years, with gestational age between 8-12 weeks without medical or surgical illness were included, while parity and socio economic status not included in the study.

100 patients – Group – I – selected for ISMN Application

100 Patients – Group – II – selected for Misoprostol application

PATIENT SELECTION CRITERIA

INCLUSION CRITERIA

- 18-40 years between 8 to 12 weeks of gestation.
- Irrespective of parity and socio economic status

EXCLCSION CRITERIA

- Gestational age more than 12 weeks
- Previous cervical surgery or scarred uterus and cervix
- Severe anemia.
- Significant medical illness such as acute liver disease /cardiovascular disease and uncontrolled seizure disorders.
- Women with adrenal disease or requiring glucocorticoid therapy
- In situ intrauterine device.

Gestational age was estimated by Last Menstrual Period (LMP) and confirmed by pelvic examination and sonography.

METHODOLOGY

Written consent of the patients were taken and if the patient was a minor, her parents consent was obtained.

50 patients were allotted to G-1A, for whom 40 mg of ISMN kept intravaginaly in the posterior fornix 3 hours prior to the dilatation and suction evacuation.

50 patients Group IB in whom 80mg of ISMN kept intravaginaly in the posterior fornix 3hours prior to the dilatation and suction evacuation.

100 patients Group II in whom misoprostol 400µg kept intravaginaly in the posterior fornix 3 hours prior to dilatation and suction evacuation.

Women were admitted one day prior to the procedure.

History taken. Local Examination (L/E), General Examination (G/E) Perabdomen (P/A) and Speculum Examination (S/E) done to rule out cervicitis/ virginitis.

Vaginal examination done and size of the uterus confirmed.

Inj. Tetanus toxoid and prophylactic antibiotics were given. Patients were instructed overnight starvation.

INVESTIGATIONS

- Urine Albumin
  Sugar
  Deposits

- Hemoglobin percentage (Hb%)
- Blood grouping and typing
- Bleeding Time (BT)
- Clotting Time (CT)
-Ultrasound pelvis

INTRAVAGINAL APPLICATION OF ISMN/MISOPROSTOL

Under Strict aseptic precautions, patient in lithotomy position 40 mg or 80mg of ISMN or misoprostol 400µg kept in the posterior fornix.

Patient was monitored for symptoms like,

Nausea

Vomiting

Head ache

Palpitation

Flushing

And treated if present.

Pulse Rate (PR), Blood Pressure (BP), Temperature monitored every half an hour.

At the end of 3 hours – shifted to Operation Theatre.

TECHNIQUE FOR DILATATION AND SUCTION EVACUATION:

Patient was asked to empty the bladder. An intravenous line (I.V) and one pint of 5% dextrose was started. Under I.V. anesthesia patient in lithotomy position with antiseptic precautions local parts was painted and draped. Vaginal Examination done. Previous finding confirmed. Sims speculum was placed in the posterior vaginal wall and anterior cervical lip was visualized and grasped with vulsellum.

The uterine sound was passed, the length of the uterine cavity and position of the uterus was noted. Hegar dilator No.8 was introduced through the os and if allowed easy passage through the internal os it was classified under nil cervical resistance. If further dilatation of the internal os was required once, then it was classified as mild cervical resistance and which did not allow No.8 Hegars as severe resistance.

Vaginal bleeding or the intracervical presence of products of conception was documented. The largest number of Hegars dilator, which could be introduced without difficulty and the ease of mechanical dilatation was assessed.

The products of conception were aspirated using a vacuum aspirator, by introducing

suction cannula of the appropriate size the products and blood were collected in the collecting jar. The Vacuum aspirator is moved over the uterine surface systematically in order eventually to cover all the surface of the uterine cavity.

Once this is done a grating sensation is felt all around the uterine cavity, no more tissue is aspirated then gentle sharp curettage is done. Methergine 0.2 mg is given intramuscularly. Bleeding is checked. Bimanual examination is repeated so as to be sure that the uterus is hard and smaller in size than before the procedure. After the procedure is over, the patients were placed in dorsal position and vital signs were recorded.

Patients were shifted to the observation room and vital signs like pulse, blood pressure and temperature were recorded every 15 minutes for first 1 hour and later every 30 minutes for 3 hours. Post operative complications like vomiting, headache, bleeding per vaginum and hypotension if present were recorded for future analysis and treated accordingly.

Patients were shifted to the family welfare ward after 3 hours.

Non immunized Rh-negative mothers were given 50 μg of anti-D immunoglobulin.

RESULTS AND ANALYSIS

200 cases opting for first trimester abortion were divided into

1) Group I A – pretreated with 40mg of ISMN (n50)
2) Group I B – pretreated with 80mg of ISMN.(n50)
3) Group III – pretreated with misoprostol(n100)

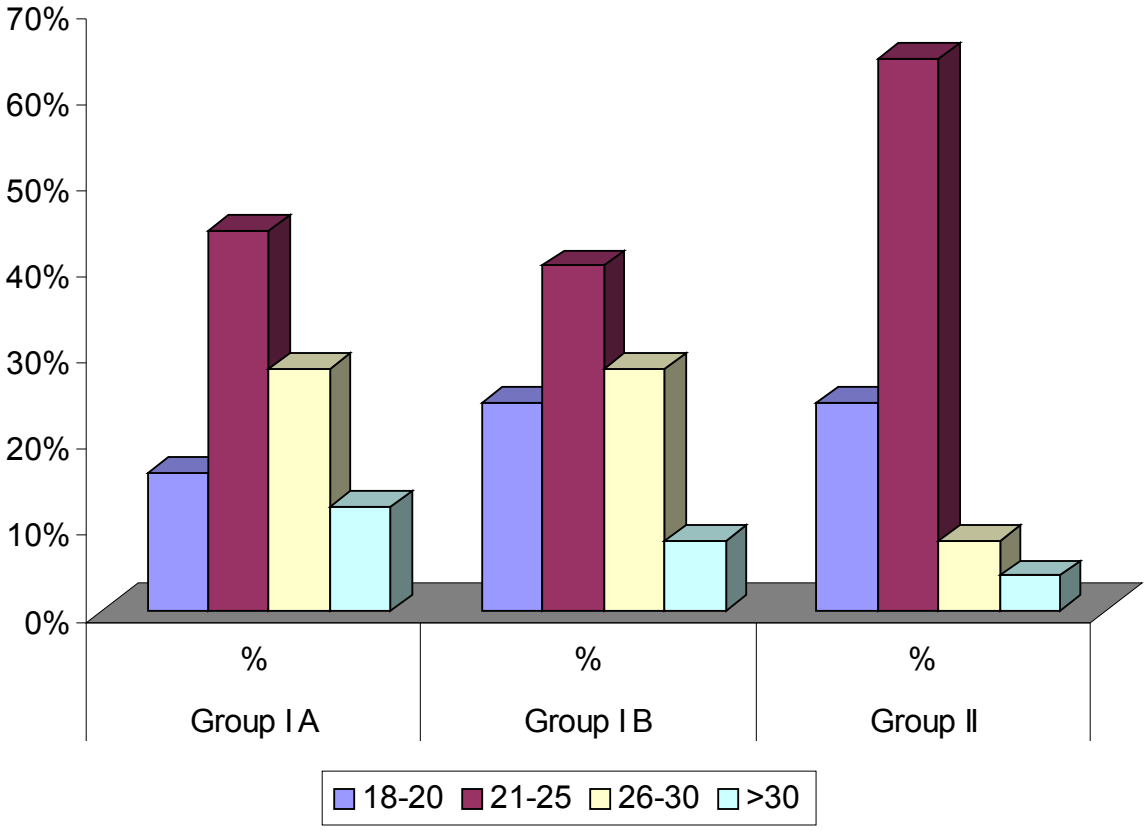
1. DISTRIBUTION OF AGE :

Table :1

Age group	Group I A		Group I B		Group II		Total	
	No	%	No	%	No	%	No	%
18-20	8	16 %	12	24 %	24	24 %	44	22 %
21-25	22	44 %	20	40 %	64	64 %	106	53 %
26-30	14	28 %	14	28 %	8	8 %	36	18 %
31-40	6	12 %	4	8 %	4	4 %	14	7%

In Group IA 72% and Group IB 68% and Group II 72% were in the age group of 21-30 years. 10% in Group I, 4% in Group II were in the age group of 31-40 years.

1. DISTRIBUTION OF AGE



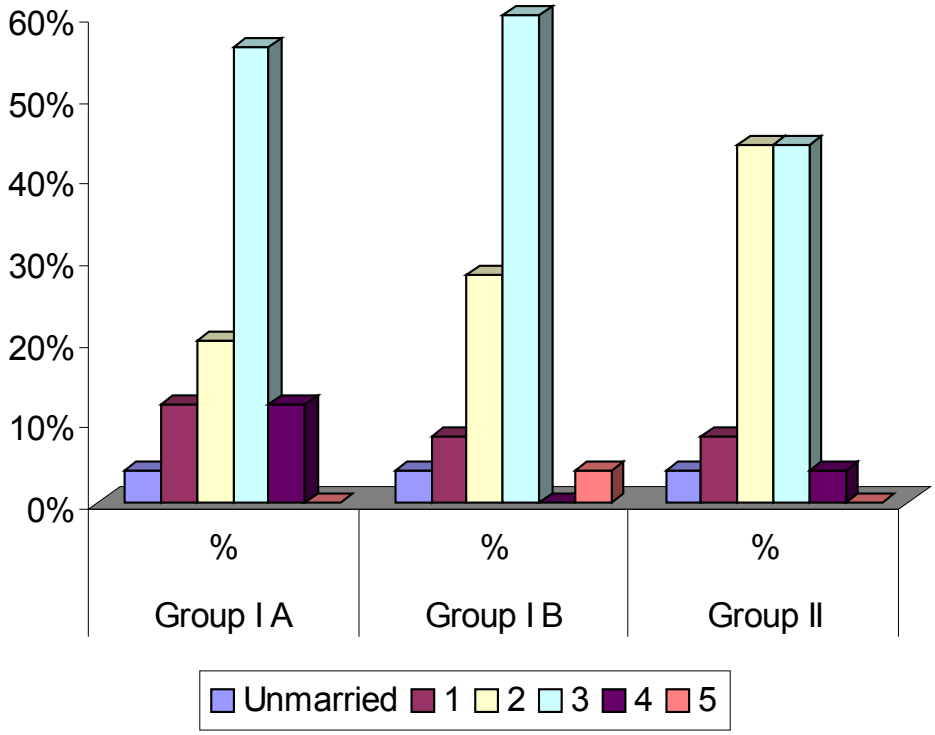
2. DISTRIBUTION OF PARITY:

Table :2

Gravida	Group I A		Group I B		Group II		Total	
	No	%	No	%	No	%	No	%
Unmarried	2	4 %	2	4 %	4	4 %	8	4 %
1	6	12 %	4	8 %	8	8 %	18	9 %
2	10	20 %	14	28 %	44	44 %	68	34 %
3	28	56 %	30	60 %	44	44 %	102	51 %
4	6	12 %	-	-	4	4 %	10	5 %
5	-	-	2	4 %	-	-	2	1 %

Group IA 76% and Group IB 88% and Group II 88% belongs to Gravida II and III.

2. DISTRIBUTION OF PARITY:



3. GESTATIONAL AGE (GA) OF THE RESPONDERS:

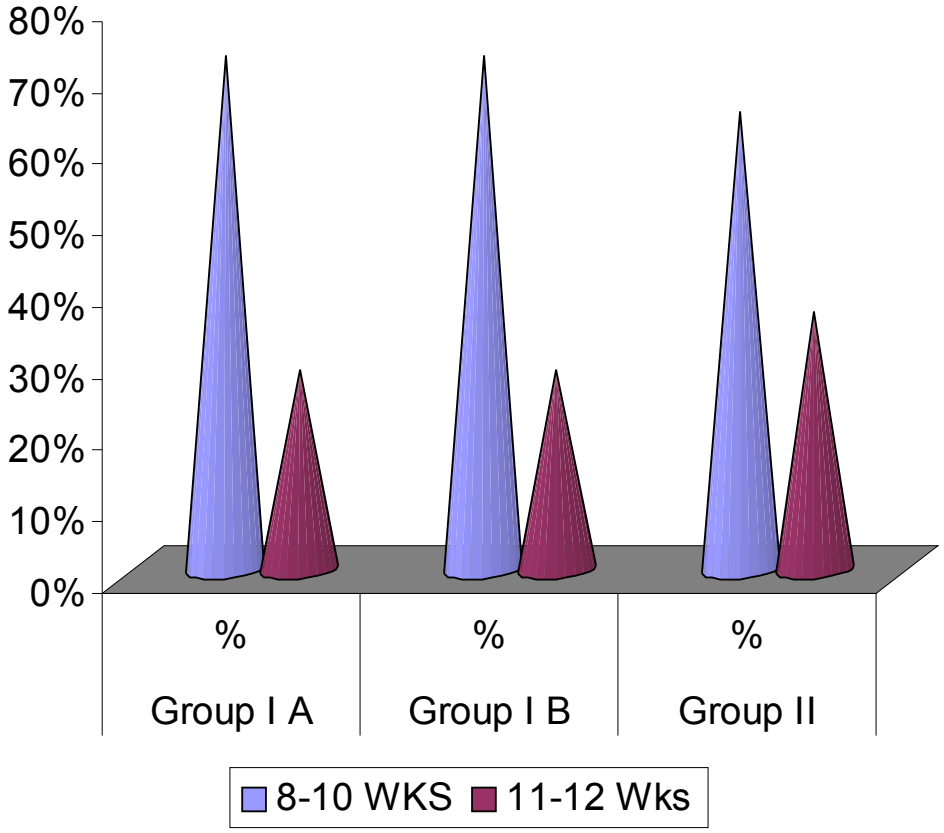
Table :3

GA	Group I A		Group I B		Group II		Total	
	No	**%**	**No**	**%**	**No**	**%**	**No**	**%**
8-10 Weeks	36	72 %	36	72 %	64	64 %	136	68 %
11-12 Weeks	14	28 %	14	28 %	36	36 %	64	32 %

GA Wise distribution :

Among the 200 cases, the cases were selected such that divided in 2 subsets based on GA with between 8-10 weeks and the other with GA between 11-12 weeks.

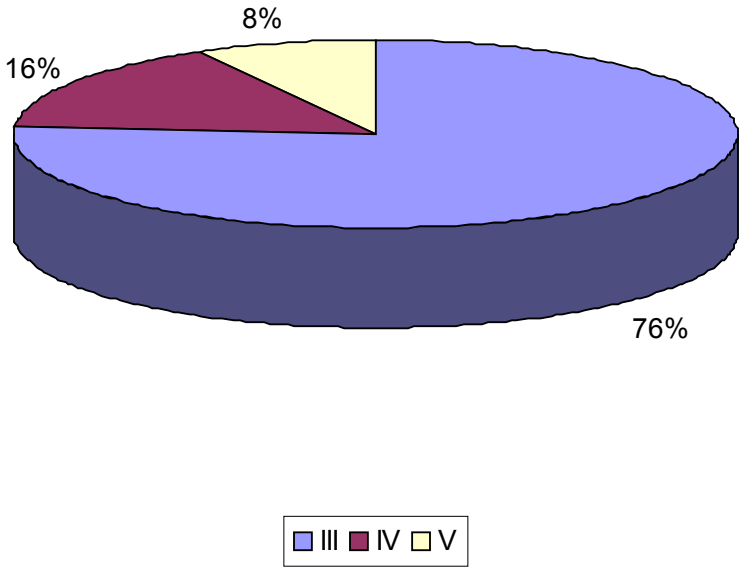
3. GESTATIONAL AGE OF THE RESPONDERS:



SOCIOECONOMIC STATUS (SES)

SES	I	II	III	IV	V
			76%	16%	8%

Most of them fall into lower socio Economic status. Patients from SES V constituted 76%,SES IV 16% SES III 8%.



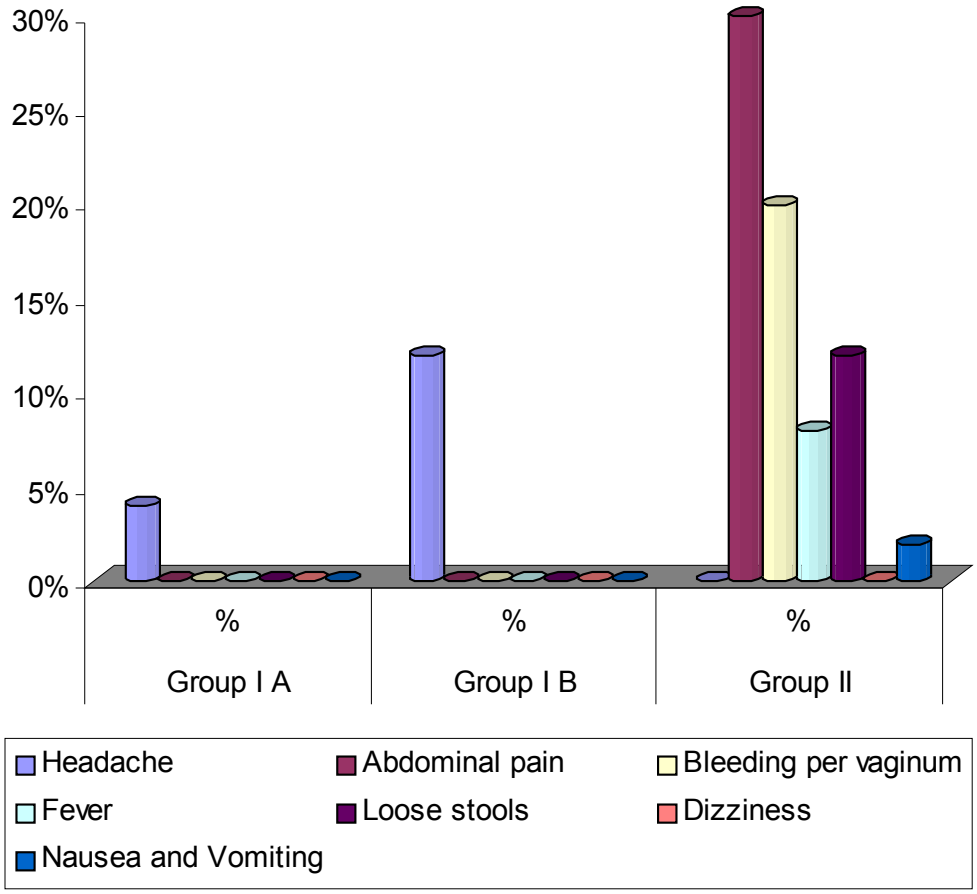
4. PREOPERATIVE SIDE EFFECTS OF THE PATIENTS

Table :4

Preoperative Side Effects	Group I A		Group I B		Group II		Total	
	No	%	No	%	No	%	No	%
Headache	2	4 %	6	12 %	-	-	8	4 %
Abdominal pain	-	-	-	-	30	30 %	30	15 %
Bleeding per vaginum	-	-	-	-	20	20 %	20	10 %
Fever	-	-	-	-	8	8 %	8	4 %
Loose stools	-	-	-	-	12	12 %	12	6 %
Dizziness	-	-	-	-	-	-	-	-
Nausea and Vomiting	-	-	-	-	2	2 %	2	1

The patients in group IA & group IB had no specific complaints except for headache constitute 8% compared to Group II where 30% had abdominal pain, 20% had bleeding per vaginum, 8% had fever, 12% had loose stools, 2% had nausea and vomiting, with a **significant p value of <0.001.**

4. PREOPERATIVE SIDE EFFECTS OF THE PATIENTS



5. CERVICAL RESISTANCE OF THE RESPONDERS:

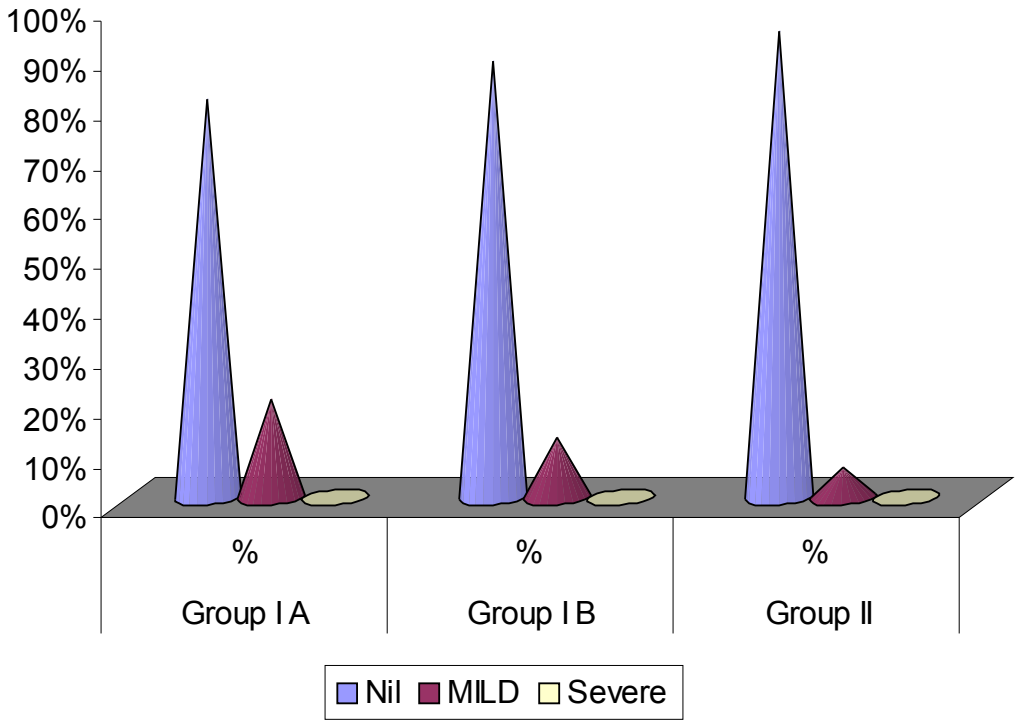
Cervical Resistance	Group I A		Group I B		Group II		Total	
	No	**%**	**No**	**%**	**No**	**%**	**No**	**%**
Nil	40	80 %	44	88 %	94	94 %	178	89 %
Mild	10	20 %	6	12 %	6	6 %	22	11 %
Severe	-	-	-	-	-	-	-	-

In Group IA 20% required further dilatation, in Group IB 12% required further dilatation, with a **insignificant p value of 0.157** between Group I A and I B

In Group II 94% did not require further dilatation.

Group IA & IB 16% and in Group II 6% required further dilatation with a **significant P value of .0330.**

5. CERVICAL RESISTANCE OF THE RESPONDERS:

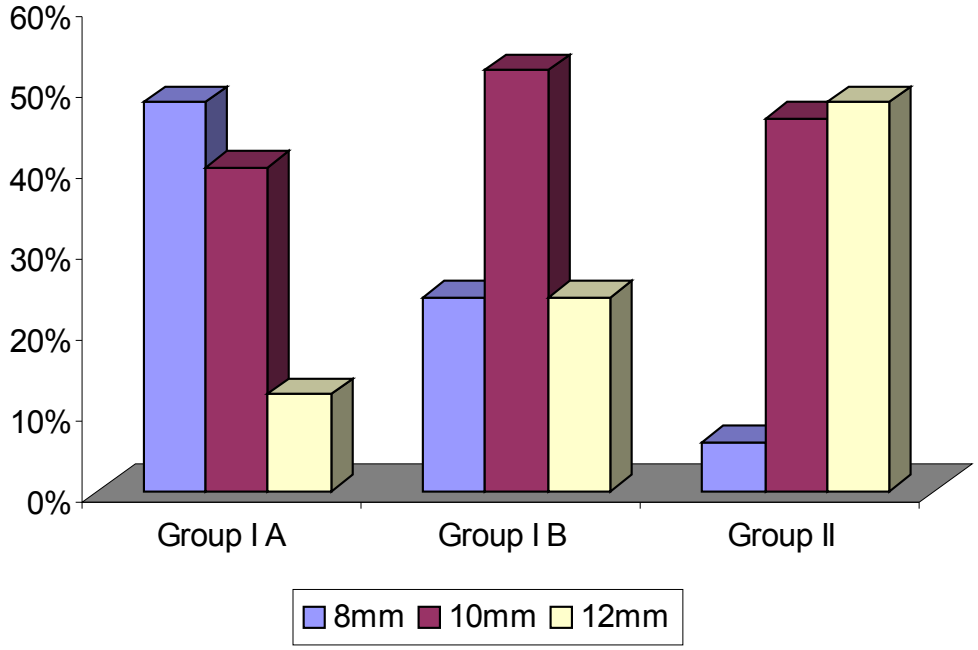


CERVICAL DILATATION

Cervical Dilatation(mm)	Group I A		Group I B		Group II		Total	
	No	%	No	%	No	%	No	%
8	24	48 %	12	24 %	6	6 %	42	21 %
10	20	40 %	26	52 %	46	46 %	92	46 %
12	6	12 %	12	24 %	48	48 %	66	33 %

In Group II patients had 12 mm dilatation in 48% of the cases,but only 18% in Group I had 12 mm dilatation with a **significant p value of <0.001.**

CERVICAL DILATATION



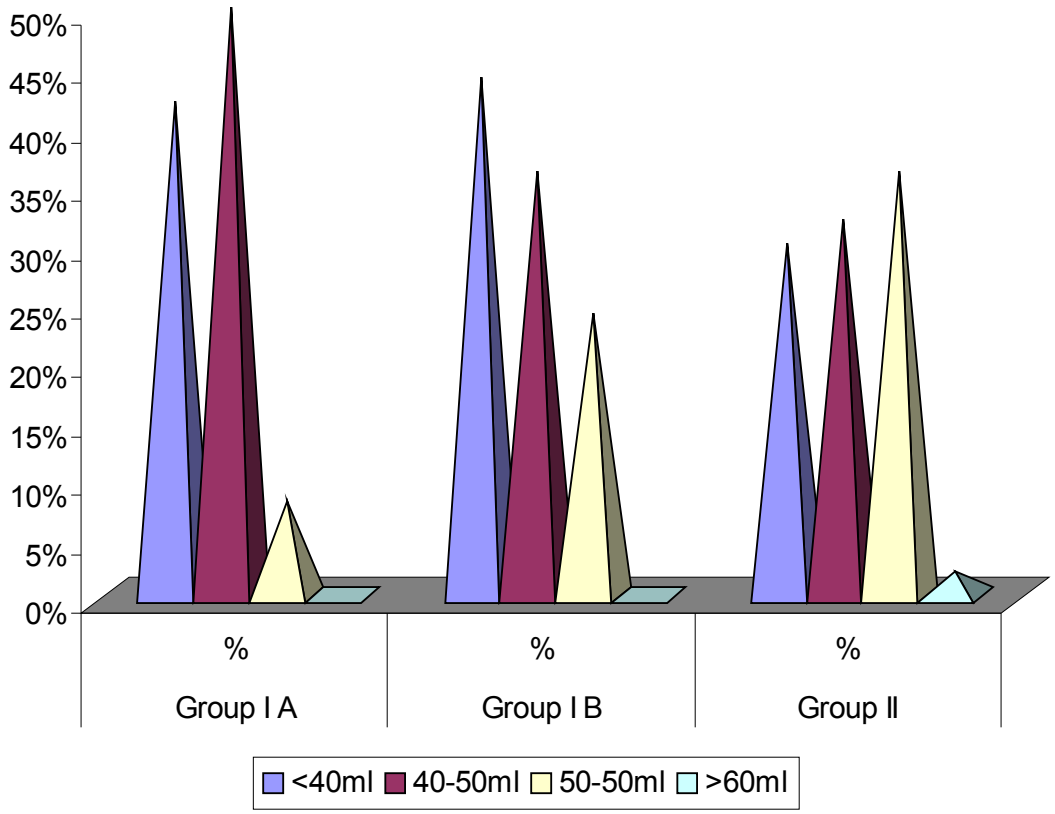
6. AMOUNT OF BLOOD LOSS

Blood loss in ml	Group I A		Group I B		Group II		Total	
	No	%	No	%	No	%	No	%
<40ml	21	42 %	22	44 %	30	30 %	73	36.5%
41-50ml	25	50 %	18	36 %	32	32 %	75	37.5%
51-60ml	4	8 %	10	20 %	36	36 %	50	25 %
>60ml	-	-	-	-	2	2 %	2	1%

In Group IA 42%, Group IB 44% had blood loss of < 40 ml.

In Group II 36 patients had 51-60ml blood loss with incidence of 36% and 2% had excessive blood loss more than 60 ml.

6. AMOUNT OF BLOOD LOSS



AMOUNT OF BLOOD LOSS ACCORDING TO GA

GROUP	GA	<40ml	41-50ml	51-60ml	>60ML

Group I A	8-10 weeks	20	55.5%	16	44.5%	-	-	-	-
	11-12 weeks	1	7.14%	9	64.3%	4	28.6%	-	-
Group I B	8-10 weeks	22	61.1%	14	38.9%	-	-	-	-
	11-12 weeks	-	-	4	28.6%	10	71.4%	-	-
Group II	8-10 weeks	30	46.8%	28	43.7%	6	9.5%	-	-
	11-12 weeks	-	-	4	11.2%	30	83.3%	2	5.5%

In Group IA 55.5% and Group IB 61.1% between 8-10 weeks of gestational age had blood loss of <40 ml.

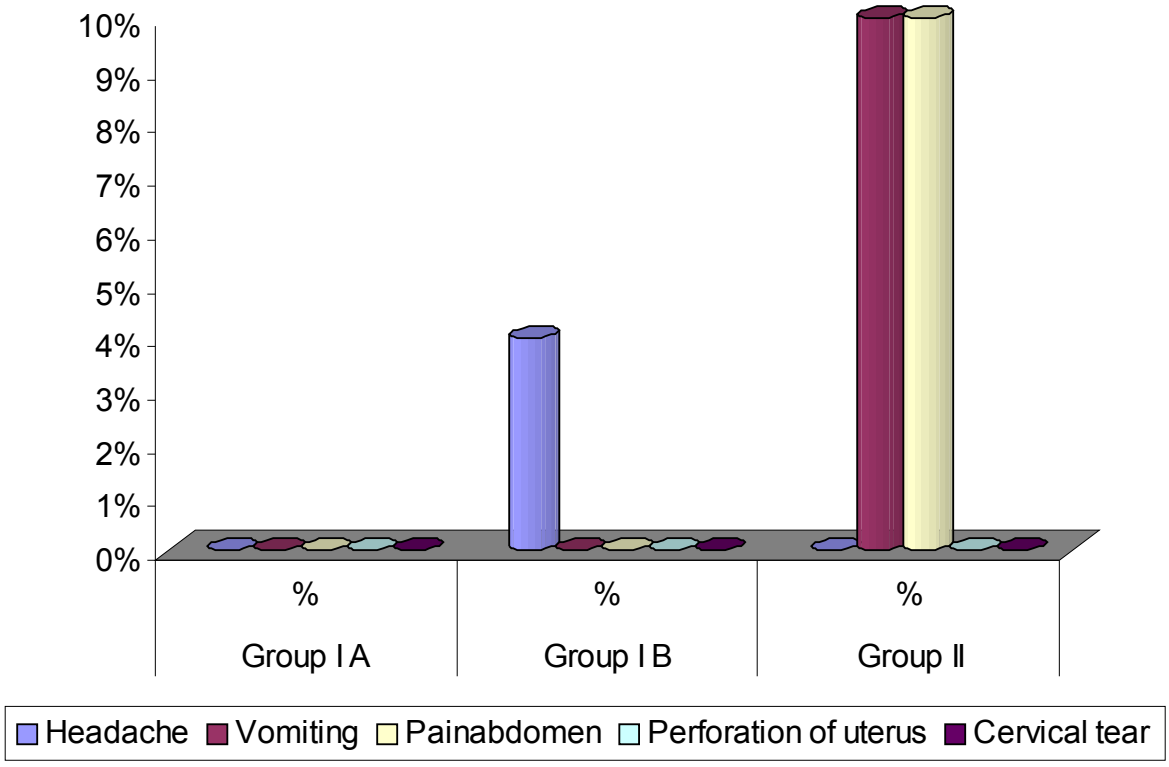
In group II 83.33% had blood loss of 51-60ml, and 5.5% blood loss of >60ml, in 11-12 weeks of gestational age.

7. POST OPERATIVE SIDE EFFECTS

Post OP Complications	Group I A		Group I B		Group II		Total	
	No	%	No	%	No	%	No	%
Headache	-	-	2	4 %	-	-	2	1 %
Vomiting	-	-	-	-	10	10 %	10	5 %
Painabdomen	-	-	-	-	10	10 %	10	5 %
Fever	-	-	-	-	-	-	-	-
Hypotension	-	-	-	-	-	-	-	-
Perforation of uterus	-	-	-	-	-	-	-	-
Cervical tear	-	-	-	-	-	-	-	-

Among the 200 cases about 2 patient in Group IB had headache.In Group II 10% of the patients experienced pain abdomen and nausea and vomiting, with a **significant p value of .00002.**

7. POST OPERATIVE SIDE EFFECTS



DISCUSSION

Cervical ripening before first trimester surgical termination of pregnancy facilitates the procedure and reduces operative morbidity. Pharmacological agents commonly used for this indications includes laminariatent, and Prostaglandin (PG) analogues. Although PG produces more effective cervical ripening, they are associated with several adverse effects including abdominal pain, nausea, vomiting and diarrhoea. The ideal cervical ripening agent should be effective and easy to administer with a low incidence of side effects.

The inflammatory mediator Nitric Oxide (NO) which has been implicated in a wide range of physiological process is a fundamental mediator of cervical ripening in animals according to Thomson AJ et al. 1997 to 1998.

We have postulated that NO can ripen the cervix before first trimester surgical termination of pregnancy by carrying out three groups randomized on 200 patients to compare the clinical effects of NO. donor ISMN 40mg & 80mg and the conventional misoprostol.

200 women were selected in random for this purpose 100 cases for 1SMN, 100 cases for misoprostol. All cases were analyzed under the following headings.

1. Age
2. Parity
3. Socioeconomic status
4. Period of gestation

5. Induction abortion interval
6. Cervical resistance
7. Cervical dilatation
8. Incidence of preoperative and postoperative complications.

AGE

The women studied in this series were in the age group ranging from 18-40 years out of which maximum women were in the age group of 21 to 30 years in both the groups and they were distributed equally for comparative study.

According to according to study by Vineeta mohindra, vaginal misoprostal for first trimester termination the study group was irrespective of the maternal age and according to **Thomson Aj et al,** (1998) study, the patients were maximum in the age group of 21-30 yrs.

Marital Status and Parity:

In the series out of 200 cases 4% in group I and 4% in group II were unmarried 76% of the patients were in gravida II and gravida III in Group IA 88% in group IB, indicates that some of Gravida III are still ignorant of the facilities available for termination of early pregnancy.

Socio Economic and Educational Status:

Most of the cases belong to lower socio economic status and poor educational status. This indicates that lower Socio economic status and educational status of people are ignorant of the methods of prevention of conception and methods of early termination of pregnancy.

Period of Gestation

In our series the cases were equally distributed between the gestational ages of 8-10 wks and 11-12wks in both groups. 68% belonged to 8-10wks of gestational age. In **Thomson AJ et al** (1997) study, the gestational age was less than 12 wks.

Induction Abortion Interval

In Group I and Group II 3 hours interval between the application of ISMN or Misoprostol and surgical termination of pregnancy similar to **Thomson et al.,** and Singh et al., and Mohindra et al., study.

Preoperative Side Effects

The side effect profile of NO, administered vaginally has been described. Their recognized side effects were noticed when administered by other routes and include headache, dizziness, post operative hypotension and tachycardia. No significant changes in maternal heart rate or systolic Blood pressure were detected, though headache was reported in 8% of study Group I, according to **Chen fc study** 15% had headache and mild hypotension.

In our study 30% had abdominal pain, bleeding pervaginum in 20% and fever, Diarrhoea, nauses and vomiting in 8%, 12% and 2% of the cases in Group II (Pretreated with misoprostol). According to **Radulovic N et al study** with misoprostol 69% had pain abdomen, 66% had vaginal bleeding ,44% had nausea and

vomiting and with ISMN 79% had headache. But according to **Vineeta Mohindra et al study** 17.3% had pain abdomen 4.7% had vomiting with misoprostol. An accumulation of Nitric Oxide (NO) donor in uterine smooth muscle would be expected to relax the myometrium there by keeping to a minimum preoperative abdominal pain.

Cervical Resistance :

Pretreatment with ISMN or misoprostol resulted in lower cervical resistance. There were no significant differences in the cervical resistance between the two ISMN group indicates that the capacity to ripen the Cervix is not dose dependent although we have assessed only two doses of the drug. But with misoprostol spontaneous expulsion of products of conception were found and had significantly greater dilatation and required less cumulative force than the ISMN group. According to **Licf, chan cw** (2003) study of comparison of ISMN with misoprostol in cervical ripening before suction evacuation more than 80% cervical ripening agent acceptable. Here also 80% in group IA and 88% in group IB and 94% in group II cervical ripening agent acceptable.

Cervical Dilatation

Though we cannot compare the dilatation produced by ISMN which is only a ripening agent with misoprostol which induces ripening and dilatation. Largest number of Hegar's dilator, which could be introduced without difficulty was assessed. Group II patients had 12mm dilatation in 48% of the cases, but only 18% in Group I with significant p value of .00000

Amount of blood loss

Amount of blood loss during the procedure varied with the gestational age. In Group IA 55.5% and Group IB 61.1% between 8-10 wks of gestational age had blood loss of <40ml.

In group II 83.33% had blood loss of 51-60ml, and 5.5% blood loss of >60ml. No women in any group required plasma volume expansion, Blood transfusion or laparotomy for perforation and no women in this study had a blood loss of greater than 500ml. There were concerns that vascular relaxation effect of ISMN might increase the operative blood loss during suction evacuation. **Thomson et al.,** did find more operative blood loss with nitric oxide donors than with misoprostol. But according to **Li cf et al.,** (2003) there were no difference in the operative blood loss between ISMN and misoprostol group.

Post Operative Complications:

This study has demonstrated that ISMN has fewer side effect when used to ripen the cervix in first trimester of pregnancy. There was headache experienced in 4% of the cases in Group I, vomiting and pain abdomen in 10% of the cases, No cases of either perforation of uterus nor cervical laceration in the study group. According to **Mohindra et al., study** 3.3% had incomplete abortion, and there was no cases of uterine perforation.

SUMMARY

The results of the analysis of the study is summed up as follows.

Majority of patients belonging to this study were in the age group 21-30 yrs, (70% in group I and 72% in the Group II). The age distribution was almost equal among the all groups.

1. 4% in group I and 4% in group II were unmarried. Majority of the women in all the groups belonged to II and III gravida.

2. The distribution of gestational age in all the three groups were same. More than half belongs to 8-10weeks of Gestational age, 72% in Group I and 64% in Groupii

3. Analysis of the preoperative side effects showed absolutely no untoward side effect on the mother in Group I except for headache constitutes 8% Group II- 30% had pain abdomen, 20% had bleeding per vaginum, 8% had fever, 12% had loose stools and 2% had nausea and vomiting.

4. Analysis of the cervical resistance showed, nil cervical resistance in 80% of the cases, mild cervical resistance in 20% and 12% in Group IA and IB, doubling the dose has been reduced mild resistance by 40%, where as group II showed 6% cervical resistance. But spontaneous expulsion of products of conception were found in the of misoprostol group only.

5. The study of the Blood loss during the procedure varied with the gestational age.

6. Only minority of the patients in all the three groups had post operative side effects, in Group IB 4% had headache and, in Group II 10% of the patients had vomiting and abdominal pain.

7. None of the patients belonging to all three groups had major complications like perforation of the uterus or cervical laceration.

CONCLUSION

This study reveals that intravaginal ISMN also ripens the cervix and it can be used as an agent for preoperative cervical ripening prior to first trimester surgical termination of pregnancy, since it fulfills almost all the criteria for an ideal agent like

- Easy availability
- Non costly
- Ease of administration
- Safety
- No undesirable maternal side effects .

The effect of ISMN is not dose dependent, even 40mg of single intravaginal application brings about adequate cervical ripening, increasing the comfort of surgery and avoiding the mechanical trauma to the cervix.

On Critical evaluation intravaginal isosorbide mononitrate is more comfortable both to the patient and doctor since it has none of the undesirable side effects like bleeding, pain abdomen, fever or loose stools when compared with conventional misoprostol.

But compared to misoprostol, ISMN is less effective in cervical ripening but less maternal side effects. Spontaneous expulsion of products of conception were found only in cases of misoprostol and it produced more pronounced cervical ripening.

To conclude this study reveals that intravaginal ISMN can also be used as an effective and safe alternative to misoprostol for cervical ripening prior to first trimester surgical termination of pregnancy when indicated avoiding misoprostol induced complications

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PROFORMA

NAME AGE IPNO

18-20	
21-25	
26-30	
>30	

ADDRESS DOA :

OCCUPATION

SES ☐ I ☐ II ☐ IV ☐ V ☐

Menstrual History Last Menstrual Period (LMP)

Expected Date of Delivery (EDD)

Regular / Irregular

Marital History Married Since

Unmarried

OBSTETRIC CODE:

History of Previous MTP Done

1. At how many weeks
2. Methods adopted

History of Previous scar

Gynecology

Obstetric

History of previous vaginal delivery

Last Child Birth (LCB)

Past History : Diabetes mellitus, systemic hypertension and history of allergies.

Reasons for MTP

Social cause

Delayed diagnosis/failure of contraception

Congenital anomalies

Medical reasons

Unwed pregnancies

General Examination

Anemic	Yes/No	Temp
Febrile	Yes/No	PR
Pedal edema		BP
CVS		RR
RS		

P/A – Size of Uterus in Weeks

8 ☐ 10 ☐ 12 ☐

Any Scar

Local Examination

Speculum Examination

Pervaginal Examination

INVESTIGATIONS

Urine Albumin Hb%

Sugar

Deposits

BloodG & T

BT

CT

Ultrasound pelvis

Time of Application

Dose

Time of MTP

Complaints after administration the drug

1. Vomiting
2. Head ache

3. Giddiness
4. Bleeding
5. Fever

Duration between the administration of the drug & MTP

Dilatation of Cervix

Hegars dilator Size 8 10 12

DURING PROCEDURE

- ❖ Resistance
- ❖ Need for further dilatation
- ❖ Amount of bleeding
- ❖ Anaesthetic complication
- ❖ Cervical laceration
- ❖ Uterine perforation
- ❖ Sepsis

RECOVERY PERIOD

COMPLICATIONS:

Vomiting Bleeding

Headache Fever Hypotension

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